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INTRODUCTION

Lymphoid reconstitution following hematopoietic stem cell transplantation

Of mice and men: progress made in HSCT immunobiology

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Experiments in the beginning 1950s had demonstrated that lethally irradiated mice could be saved by intravenous injection of bone marrow cells from other mice. This lent support to a previously formulated hypothesis that under these experimental conditions donor-derived cells repopulate the bone marrow and subsequently the lymphoid tissues. Since those early days, allogeneic hematopoietic stem cell transplantation (HSCT) has evolved as a clinically effective, life-saving therapy of choice for an increasing number of malignant and non-malignant blood disorders. Following allogeneic HSCT, a swift and complete rebuilding of the innate and adaptive immune system is critical for the successful outcome. The recovery of the T-cell compartment relies on two independent pathways that act in parallel: (1) the expansion of mature donor-derived peripheral T-cells included in the graft and (2) the *de novo* production of naïve T-cells in the thymus from hematopoietic precursors. The latter pathway assures the continuous generation of a population of T-cells that expresses a diverse repertoire of T-cell antigen receptor specificities. The formation of these T-cells is, however, curtailed by the usual need for pre-transplant chemo-radiotherapy because this treatment alters the cellular architecture and composition of the thymus. HSCT-related adverse events such as the development of graft-versus-host disease (GVHD) further hinder the formation of T-cells. The resultant delay in the development of naïve T-cells is in turn associated with opportunistic infections, the reactivation of latent viral and parasitic infections, chronic inflammation, and autoimmunity.

The essentials in HSCT biology were first defined by laboratory observations and animal studies. Specifically, the experimental transfer of different populations of hematopoietic cells using diverse conditions helped to define the cellular and molecular mechanisms that control the generation and maintenance of the hemato-lymphopoietic system. At the same time, differences in the ease of engraftment identified genetic factors to play a decisive role in bone marrow transplantation since highly inbred strains were more easily engrafted when compared to mice that had been given bone marrow from foreign strains. Finally, work also done in the late 1950s and in the 1960s began to disclose the essential function of the thymus for the normal development of the immune system.

Substantial progress has been made over time with regards to our understanding of the thymic mechanisms that shape the generation of T-cells and that influence the outcome of HSCT. This current issue of Seminars in Immunopathology focuses on recent and exciting advances achieved that relate to thymic function under steady-state conditions and to the post-transplant reconstitution of the hematopoietic system in general and that of the T-cell compartment in detail. The contribution by D. A. Zlotoff describes recent work identifying in mouse and man the phenotype of blood-borne precursors and the molecular mechanisms by which these cells access the thymus to contribute to the formation of T-cells. The transcriptional mediators that control T-cell lineage development and the thymic environmental signals necessary for lineage commitment are discussed in the article by T. Taghon. The review by T. M. McCaughtry highlights recent cellular and molecular findings that shape the antigen receptor repertoire during intrathymic

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T-cell development. In the article by J. Plum, different in vitro and in vivo experimental models are discussed that allow both the generation and analysis of human T-cells. The contribution by J. Storek describes the reconstitution of the different cellular compartments of the innate and adaptive immune system in humans following HSCT. The consequences of graft-versus-host disease on the thymic microenvironment and its impact on T-cell development are discussed in the review by W. Krenger. Strategies for reconstituting and boosting T-cell based immunity and tactics for the adoptive transfer of committed T-cell precursor as means to accelerate and improve T-cell reconstitution following HSCT are discussed in the contributions of A. P. Chidgey and of A. M. Holland, respectively. Finally, the review by A. Velardi discusses recent experimental results on the benefit of natural killer cell alloreactivity in HSCT and their potential for translation to the clinics.